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Linking Innate Immunity and Chronic Antibody-Mediated Allograft Rejection

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Abstract

Purpose of the Review—To summarize recent findings linking donor-specific antibodies with innate immunity resulting in chronic allograft rejection.

Recent Findings—Studies in recent years have highlighted the problem of donor-specific antibodies (DSA) with both acute and chronic allograft rejection. Since chronic rejection is the leading cause of graft failure, this review centers on the contribution of three areas of innate immunity of particular recent focus: complement, NK cells, and macrophages. Recent advances in understanding the diverse role that complement components play both in directly allograft injury and indirectly contributing to enhanced alloreactivity. NK cells also have emerged as an additional innate response that directly links DSA with chronic graft injury. Finally, recent studies identify alternatively activated macrophages as an additional arm of innate immunity contributing to chronic allograft rejection.

Summary—Chronic allograft rejection involves a significant contribution of DSA and differing pathways of the innate immune system. However, key issues remain unresolved. Firstly, it is not always clear which of these varied sources of innate immunity contributing to chronic rejection are antibody dependent. Moreover, it is not yet clear if these innate pathways represent independent routes of chronic rejection or rather act in concert to mediate allograft injury.

Keywords

innate immunity; antibody-mediated rejection; chronic rejection; allograft immunity

Introduction

Despite the fact that chronic rejection is the leading cause of eventual allograft loss [1]** there remains a need for better understanding of this constellation of responses and the development of corresponding therapeutic interventions to mitigate such graft injury. It is

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Conflicts of Interest

The authors have no conflicts to declare.

clear that the development of donor-specific antibodies (DSA) is a major indicator associated with accelerated chronic rejection and graft loss, putatively through a process of antibody-mediated rejection (AMR) [2–4]. The significance of antibodies in allograft rejection is also reflected in animal studies, such as those showing that adoptive transfer of DSA can restore acute cardiac allograft rejection in B cell-deficient mice [5]. While DSA can contribute to both acute and chronic allograft injury, this review will focus primarily on chronic allograft rejection due to the clinical significance of this response in reducing allograft survival. Unfortunately, chronic allograft injury in general and antibody-mediated rejection (AMR) in particular can be confounding to define mechanistically both due to the challenge in defining this amalgamation of pathologic features and unraveling the potentially wide variety of innate and adaptive immune pathways contribute to these responses. While there are several important facets of innate immunity that may contribute to AMR, this review will focus on developments involving complement, NK cells, and macrophages due to a particular recent focus in these areas Moreover, due to the capacity to perform mechanistic studies in animal models, several aspects of this discussion will focus on experimental pre-clinical studies. Taken together, the focus of this review is to describe recent studies that implicate specific innate immune pathways as links between DSA and the expression of AMR in chronic allograft rejection.

Complement - traditional and progressing views regarding AMR

Probably the most common concept linking antibodies and innate immunity, including those involving AMR, is that of complement activation presumably contributing to allograft injury. Indeed, a recent extensive metanalysis of many studies strengthened the concept that complement activating DSA is an important correlate with increased graft injury [6]. It has become clear that complement components have both direct and indirect routes for contributing to AMR. A common view is that antibody binding of endothelial cells (EC) leads to complement activation, EC activation, and potential cell injury. Indeed, C4d deposition in the graft is known to associate with chronic injury and is increasingly considered a surrogate marker for AMR [3]. More recently, a study concluded that C5b9 deposition in glomerular capillaries also is associated with reduce kidney allograft survival [7]. However, despite this association of complement activity with AMR, a key question is how complement activation actually results in vascular injury or other forms of chronic rejection. There are clearly direct effects of complement components on graft dysfunction. For example, in a renal disease model, C3a can trigger a kidney tubular epithelial-to-mesenchymal cell transition that can result in chronic tubular fibrosis [8]. Other recent studies indicate that antibody-triggered complement membrane attack complexes result in direct Rab5-mediated NF-kappaB activation in EC [9]• with inflammasome induction resulting in production of pro-inflammatory cytokines such as IL-1 [10]. Interestingly, this type activation alone does not appear to directly result in pronounced EC death, supporting the idea that complement-mediated signals can activate vascular endothelium and poise such cells for additional routes of innate and adaptive injury, some of which are described below.

It has become increasingly apparent over recent years that complement components also have indirect effects on graft injury by promoting a complex and diverse enhancement of adaptive alloreactivity [11]. Complement-dependent activation of EC activation may

enhance the known capacity of these cells to induced alloreactive CD8 T cells [12]. Moreover, there are important alternative means through which complement signaling enhance both T cell and B cell alloimmune responses. For example, complement C3a and C5a signaling is known to enhance CD8 T cell reactivity [13,14]. An intriguing recent study further expands the role of complement in promoting alloimmunity by showing that C5a receptor 1 signaling can play an important role in the differentiation of follicular helper cells (Tfh) that in turn activate B cells to promote antibody production [15] •. One can envision a vicious cycle of complement receptor signaling events that result in both EC-dependent and -independent enhancement of adaptive alloimmunity resulting in CD8 and Tfh activation, the latter of which may result in even more DSA production. Taken together, complement activation clearly has the capacity to trigger direct dysfunction on graft vasculature and promote adaptive immunity through routes that may not be directly linked to DSA. As such, it may not be surprising that chronic rejection often manifests as a blend of features associated with both AMR and T cell-mediated rejection as reflected by recent updates in the Banff criteria for defining acute and chronic rejection [3]•[9].

NK Cells: a prototypical link between adaptive and innate immunity in AMR?

The past several years has seen a dramatic emergence in studies indicating the significance of NK cells as innate mediators of AMR. Initial molecular phenotyping indicated a strong signature of NK cell transcripts in clinical kidney AMR [16], an observation that has been replicated in subsequent analyses of AMR in both kidney [17] and heart [18] allograft recipients. Moreover, reductionist pre-clinical studies probably provide the strongest current evidence directly linking DSA and NK cells in mediating chronic allograft rejection. Interestingly, although there is little doubt that complement activation contributes to AMR and chronic rejection, initial pre-clinical mouse studies by Hirohashi *et al* [19] indicated that adoptive transfer of DSA to immune-deficient ($rag1^{-/-}$) bearing cardiac allografts resulted in arterial injury that was complement independent, suggesting either that DSA directly injured the graft or that other innate immune mechanisms contributed to chronic rejection. A key follow-up study from this group showed that NK cells were essential for triggering vascular in this mouse model of AMR [20]; neither NK cells or DSA alone were sufficient to trigger significant chronic rejection. Moreover, a direct link between DSA Fc-receptor binding to NK cells was suggested by the finding that DSA F(ab')2 fragments that could not mediate effective chronic rejection [20]. NK cells also contribute to AMR in kidney allografts in mice, but these cells appear to be more important for acute [21] than for chronic [22] rejection in this model. Thus, the contribution of NK cells to AMR is not limited to cardiac allograft models in mice.

An important question centers on how NK cells might mediate allograft injury. Subsequent dissection of the model developed by Hirohashi *et al* [19] indicated that NK cell-derived IFNγ was essential for cardiac allograft vascular remodeling [23]. This result was intriguing since prior studies found that IFNγ was sufficient to induce to induce arteriosclerosis independently of participating leukocytes [24]. Thus, a simple proposition could be that NK-derived IFNγ is sufficient to drive vascular pathology. However, Lin *et al* [23] also found

that IFNγ was not sufficient for inducing vascular pathology; NK cells also required the expression of cytotoxic mediators, either perforin of FasL (CD95L). This additional finding suggests that NK cells mediate chronic AMR through a combination of contact-dependent cytotoxicity *and* local IFNγ production. These requirements for NK cell-mediated effector function in chronic AMR are remarkably similar to other studies of CD8 T cell mediated rejection in which both IFNγ [25] and contact-dependent cytotoxic mechanisms [26] are required for rejection. This may be significant in that very similar effector pathways may be contributing to both acute T cell-mediated rejection and NK cell-mediated AMR, making the molecular distinction between these types of rejection challenging.

Macrophages, chronic rejection and AMR

Ironically, while monocytic cells have long been associated with acute and chronic allograft injury, our perception is that this class of innate cells tends to be under-appreciated for their potential role in acute and chronic AMR. There is a long-standing correlation between macrophage accumulation and chronic allograft injury [27]. Importantly, macrophages comprise a substantial proportion of graft-infiltrating cells in chronically rejecting allografts [28] and correlates with poor outcomes in clinical kidney [29] and heart [30] allograft survival. The significance of macrophages in experimental models of chronic rejection is illustrated by the finding that attenuate this response, indicating that these cells can play an essential role in triggering graft injury [31]. A confounding issue is there is a broad heterogeneity of functional and molecular phenotypes of activated macrophages [32,33]. In broad terms, the variability of macrophages range from the more pro-inflammatory M1-like phenotype to the alternatively activated, anti-inflammatory M2-like property [32]. While M1-like macrophages may contribute to acute rejection, recent mechanistic studies provide strong evidence that M2-like macrophages play a key role in chronic rejection.

Firstly, M2-like macrophages are a substantial component of allografts undergoing chronic vascular injury [27,34]. Also, Smad-3-dependent transition of monocytes to myofibroblasts with an M2-like macrophage phenotype can occur during chronic kidney allograft rejection [35]. Importantly, while M2-like macrophages are correlated with chronic rejection, recent studies make a more causal connection between this type of alternatively activated macrophages and chronic rejection. Inhibition of the P2X7 receptor (P2X7R) of adenosine triphosphate-gated ion channels inhibits M2 macrophage function and corresponding chronic rejection [36]. However, the P2X7R receptor is not macrophage-specific, so the singular role for this cell type in chronic rejection was not clear. An elegant recent study indicates that genetic impairment of mTOR-dependent M2 macrophages but not pro-inflammatory Traf6-dependent M1 macrophages results in reduced allograft vascular injury [37]**. This later study provides evidence more directly implicating M2-like macrophages as mediators of chronic rejection.

Despite strong evidence linking macrophage activity with chronic allograft rejection, an obvious question centers on the degree of connection between DSA and macrophage-dependent graft vasculopathy and fibrosis is much less clear. That is, in most of the studies described above, the requirement for DSA was not established as a link to macrophage-dependent pathology. Moreover, there is increasing evidence of an unanticipated innate

allorecognition by monocytic cells [38–40], an important concept recently reviewed by Lakkis and Li [41]•. This unanticipated type of macrophage allorecognition may lead to macrophage effector function that conceivably contributes to acute or chronic allograft injury [42] that may not at all depend on DSA. Also, CD4 T cells recognizing alloantigens via 'indirect' (host MHC-restricted) can trigger vascular injury independently of antibodies or CD8 cells [43], a pathway that also could conceivably involve antigen presentation by macrophages. Thus, while macrophages clearly contribute to chronic allograft rejection, the exact signals that drive this response and the range of interactions between macrophages and other innate and/or adaptive immune cells and DSA leading to macrophage-dependent graft dysfunction requires further understanding.

Conclusion: Important unanswered questions

While there is clear evidence that DSA and innate immunity in the form of complement, NK cells and macrophages all contribute to chronic allograft injury, there are key questions that remain unanswered. While the term antibody-mediated rejection is commonly used, this phrase can imply a mechanism in which DSA may directly result in acute or chronic allograft injury. It is imperative to note that there is considerable variability in the link between DSA and chronic rejection. Although de novo generation of DSA correlates with increased risk of allograft dysfunction on the population level, DSA levels is not always a reliable measure of what is classified as chronic rejection across varied organ types [44–47]. That is, several such studies suggest that chronic rejection can occur in the absence of pronounced DSA or that the presence of DSA does not always result in chronic rejection. These exceptions are important because they illustrate that defining a unifying mechanism of AMR and the contribution of innate immunity in this process is very challenging. In some cases, DSA may play a causal role in triggering innate immune reactivity to the transplant while in other situations, such antibodies may simply be a marker of other pathways of T cell dependent reactivity. In addition, it is often not clear whether innate immune reactivity to the allograft is always involves DSA. As an example regarding complement deposition in the allograft, the association between C3d and AMR is not always observed [48] and there is clear evidence of apparent AMR without detectable C4d deposition [49]*. Thus, there is an ongoing need to establish greater clarity regarding the requirement for DSA in the types of innate responses described above.

A final important consideration is determining whether different forms of innate reactivity in chronic rejection occur independently or rather work in concert. Gene expression profiling of hearts undergoing putative clinical AMR indicates the simultaneous presence of activated endothelium, NK cells, macrophages, and IFNγ, comprising a wide spectrum of elements associated with innate pathways of chronic rejection described above [18]. As such, it is presently difficult to know which of these pathways may be dominant or rate-limiting in mediating graft injury. Examples described above illustrated examples of innate pathways of chronic rejection that did not have any obvious requirement for other types of innate responses (e.g, NK cells interacting with macrophages). This issue has important therapeutic implications. For example, if complement-, NK cell-, and macrophage-dependent allograft injury can all occur independently of each other, than targeting a single arm of the innate immune response may be of limited benefit. However, if these pathways interact with one

another, then there is greater optimism for targeting one or more of these pathways to attenuate AMR and chronic rejection.

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Key Points

- Donor-specific antibodies (DSA) are associated with exacerbated acute and chronic allograft rejection with chronic rejection being a leading cause of graft failure.
- DSA are likely to invoke innate immune responses that contribute to chronic allograft injury.
- Recent studies have highlighted the mechanisms of complement, NK cells, and macrophages as innate immune system mediators of chronic rejection.
- Further studies are necessary to provide clear links between DSA and innate mechanisms of chronic rejection.